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(54) Title: PHARMACEUTICAL COMPOSITIONS HAVING REDUCED BITTER TASTE

(57) Abstract: Masking the taste of bitter pharmaceuticals in dispersible compositions is difficult. A novel formulation for dispersible compositions has been found where the bitterness of active ingredients is reduced and the amount of lipid in the formulation is minimised thereby reducing the retardation affect lipids have on release of the active ingredient from the composition. The invention is particularly relevant to basic bitter tasting pharmaceuticals such as macrolide antibiotics, especially erythromycin, roxithromycin, azithromycin, and clarithromycin.

PHARMACEUTICAL COMPOSITIONS HAVING REDUCED BITTER TASTE

FIELD OF INVENTION

This invention relates to the masking of the taste of bitter tasting pharmaceuticals. In particular, the invention relates to the taste masking of dispersible compositions containing bitter tasting basic active ingredients, especially macrolide antibiotics such as erythromycin, roxithromycin, azithromycin, clarithromycin, and others.

BACKGROUND

Overcoming the bitterness of certain pharmaceutical active ingredients is a continuous challenge for formulation scientists. The challenge is even greater for dispersible pharmaceutical compositions, in contrast to other types of formulations such as capsules and non-dispersible tablets. Dispersible pharmaceutical compositions have the advantage of being easier to swallow than capsules or tablets. This advantage is of particular benefit to paediatric and geriatric patients who prefer easy-to-swallow preparations.

A number of techniques are known for masking the bitter taste of active ingredients in pharmaceutical powders, granules and dispersible tablets intended for oral use. These include coating the powders or granules, microencapsulation of the active ingredient, and complex formation of the active ingredient. However, these techniques can be limited by the number of excipients required, the amounts of each component needed, the level of complexity of manufacturing processes, and the use of volatile organic solvents. There are often also scale-up problems associated with such complex techniques.

French patent no. FR 2793690 (Dominique) describes the use of high concentrations (up to 20 %) of sweetening agents, other than sugars, in dispersible macrolide compositions. However, sweetening agents such as aspartame, saccharine, and ammonium glycerrhizinate have distinctive and

undesirable after tastes themselves. They also each have other side effects when used in high concentrations. These traditional sweeteners are, in any case, not effective in masking the taste of powerfully bitter pharmaceutical actives such as azithromycin.

US patent no. 5,609,909 (Meyer) discloses the use of prolamine fractions of grain proteins applied as coatings over the drug core using a water-insoluble oil or wax as a plasticizing agent. This method has limited application for immediate releasing macrolide suspensions. Organic coating materials are required for this method as well as equipment such as a Glatt-Wurster fluid bed coater.

US patent no. 6,153,220 (Cumming) discloses the spray-drying of an active drug with a cationic copolymer, synthesized from dimethyl amino ethyl methacrylate and methacrylic acid esters, to mask taste. Organic solvents are used in this method. Additionally, there is a limit to the drug dose that can be used, e.g. a ratio of drug to polymer of up to 1:6.

pH dependent polymers often used for enteric coatings or in delayed release preparations have been used for taste masking. US patent no. 5,409,711 (Mapelli) discloses the use of a polymeric membrane which is soluble above pH 5 for the taste masking of granules. An acidic substance is added to the composition to prevent the dissolution of membrane in the mouth. Dispersible granules obtained by this process release the drug only above pH 5.

An important disadvantage of formulations prepared by encapsulation and spray drying is that volatile organic solvents such as methylene chloride, chloroform, cyclohexane, carbon tetrachloride, methylethyl ketone, acetone, ethyl alcohol, methyl alcohol or isopropyl alcohol may be needed to dissolve the coating agent. Such solvents are regarded as environmentally unfriendly and it is necessary to eliminate them from products or reduce the amounts of them to acceptable levels.

Alkaline substances used to reduce drug release from encapsulated microcapsules have been evaluated in pharmaceutical mixtures. US patent

no. 4,656,027 (Sjoovist) discloses the use of an alkaline substance encapsulated with a drug and an hydrophobic polymer to mask the taste of bitter substance. Again, the use of organic solvents for encapsulation is undesirable for environmental reasons. In addition, there is a limit on drug loading and there are difficulties with the production of large batches.

US patent no. 5,633,006 (Catania) utilizes alkaline earth oxides, alkaline earth hydroxides and alkaline hydroxides for taste masking bitter pharmaceutical compositions containing the macrolide antibiotic azithromycin. Azithromycin tends to adsorb to the alkaline earth oxide resulting in reduced bitterness of the compositions. However, in some cases such adsorption alters the drug release kinetics. The dosage forms suggested for this method are limited to chewable tablets and oral suspensions.

Formulation scientists working on macrolide antibiotics have used functional polymers with basic oxides to provide taste-masked products. US patent no. 5,707,646 (Yajima) discloses the use of a functional polymer in conjunction with a substance having a low melting point, a basic oxide, and a sugar alcohol for taste masking. However, the requirement of spray drying technology, low drug loading and high amounts of fatty acid ester are limitations on this method.

US patent no. 5,792,373 (Yajima) utilizes a polymer that is soluble in the stomach together with a monoglyceride in the β-crystal form to mask the taste of pharmaceutical compositions for oral administration. However, the high proportion of monoglyceride with respect to the active ingredient retards drug release. Limiting factors for this method include the use of functional polymers that are unstable at high temperatures, low drug loading, and the process of spray drying.

A taste-masked granule comprising a complex between clarithromycin and carbomer is described in US patent no. 4,808,411 (Lu). The aqueous granulation of the clarithromycin carbomer complex is described in US patent no. 5,919,489 (Gerhardt). However, the number of pharmaceutical

manufacturing processes and techniques needed, such as complexation, granulation, and drying, make this method undesirable.

A feature of many taste masking formulations is the incorporation of a lipid such as a fatty acid ester. However, the proportion of lipid in known taste masking formulations is comparatively high and is typically greater than 20 % by weight of the active ingredient.

For example, US patent no. 5,635,200 (Douglas) describes a taste masking composition of the drug ranitidine where a ranitidine core is coated with a lipid. The amount of lipid used is greater than 20 % by weight. It is well understood that the amount of lipid needed when dispersing a drug through the lipid is significantly greater than the amount of lipid needed when merely coating a drug core with the lipid. Therefore, if dispersing ranitidine through a lipid, significantly greater than 20% by weight lipid in the composition would be needed.

US patent no. 5,380,535 (Geyer) describes a chewable tablet where an unpalatable drug is dispersed or dissolved in a lipid. The amount of lipid used is 5-50 % by weight of the composition. However, these proportions by weight of the composition equate to much greater proportions by weight of the active ingredient. Dispersible formulations, compared with chewable tablets, typically require an even greater amount of lipid.

The primary purpose of including a lipid in a taste-masking formulation is to limit release or dissolution of the active ingredient in the mouth (in the case of a chewable tablet) and to limit release or dissolution of the active when added to water or when in the mouth (in the case of a dispersible composition) where it will be tasted. Therefore, a minimum level of lipid in the composition of 20 % is typically required. However, the consequence of a high level of lipid is the retardation of drug release from the composition leading to a delay in absorption of the active ingredient into the blood stream. There is therefore a need for a dispersible composition which effectively masks the bitter tastes of certain active ingredients while not suffering from problems of retarded release of the active ingredient from the composition when used by a patient.

The applicant has now found a simple, reproducible, novel drug delivery system for dispersible pharmaceutical compositions with reduced bitterness for bitter alkaline drugs and which contains a surprisingly low level of lipid.

The invention relates to the use of lipids, such as fatty acid esters, an alkaline substance and a surface active agent to form a granular matrix that reduces the bitterness of an active ingredient. The dispersible composition includes granules of the active ingredient and granules of a fast disintegrating diluting agent.

It is an object of the invention to provide a dispersible pharmaceutical composition containing a low level of lipid which goes at least some way to masking the taste of bitter tasting active ingredients, or at least to provide a useful alternative.

STATEMENTS OF INVENTION

In a first aspect of the invention there is provided a dispersible pharmaceutical composition including:

(i) a bitter tasting active ingredient;

(ii) a lipid granulating agent in the amount of 1 to 16 % by weight of the active ingredient; and

(iii) an alkaline agent in the amount of 1 to 20 % by weight of the active ingredient;

where the bitter taste of the active ingredient is partially or completely masked.

It is preferred that the bitter tasting active ingredient is a macrolide antibiotic, more preferably the macrolide antibiotic is selected from erythromycin, clarithromycin, roxithromycin, and azithromycin, including any solvate or hydrate thereof. The azithromycin employed is preferably in form of isostructural pseudopolymorphs which exhibits superior dissolution properties as disclosed in Croatian Patent Application No. P20020231A.

The lipid granulating agent is preferably in the amount 2 to 8 % by weight of the active ingredient.

The lipid granulating agent may be any fatty acid ester, oil, fat, or wax. However, the lipid granulating agent is preferably selected from glycerol mono-, di-, and tri-stearate, glycerol mono-, di-, and tri-palmitostearate, glycerol mono-, di-, and tri-behenate, glycerol mono-, di-, and tri-oleate, hydrogenated castor oil, a cetomacrogol emulsifying wax, carnuba wax, cetyl alcohol, and a cetyl ester.

It is preferred that the alkaline agent is in the amount 2 to 12 % by weight of the active ingredient. A variety of alkaline agents may be used, but preferably the alkaline agent is selected from sodium carbonate, potassium carbonate, sodium phosphate, potassium phosphate, sodium hydroxide, and potassium hydroxide.

It is preferred that the composition further includes a surface active agent in the amount of not more than 2 % by weight of the active ingredient. The surface active agent is preferably selected from sodium lauryl sulphate, docusate sodium, polysorbates, and sorbitan fatty acid esters.

It is also preferred that the composition further includes a diluting agent in the amount of 5 to 60% by weight of the total composition. The diluting agent is preferably selected from cellulose, microcrystalline cellulose, lactose, mannitol, sorbitol, starch, calcium carbonate, dibasic calcium phosphate, silica, and pre-gelatinized starch.

Preferably the diluting agent is prepared in the form of granules using a combination of microcrystalline cellulose and starch in a ratio from 1:3 to 3:1, and a water insoluble cellulose. The water insoluble cellulose is preferably ethyl cellulose in the amount of 2 to 10 % by weight of the granules. The microcrystalline cellulose and starch are preferably in a ratio from 1.25:1 to 2:1.

It is further preferred that the composition includes a disintegrating agent in the amount of 1 to 12 % by weight of the total composition. The disintegrating agent is preferably selected from carmellose sodium, croscarmellose sodium, sodium starch glycolate, crospovidone, aminoalkyl methacrylate copolymer E, and Polacrillin potassium.

In a preferred embodiment of the invention the disintegrating agent is cationic polymer aminoalkyl methacrylate copolymer E.

It is also preferred that the composition further includes a sweetening agent in the amount of 1 to 10% by weight of the total composition. The sweetening agent is preferably selected from aspartame, coated aspartame, ammonium glycerrhizinate, saccharin sodium, acesulfame potassium, and sugars.

Preferably the composition further includes one or more flavouring agents in the amount of 1 to 6% by weight of the total composition. The one or more flavouring agents are preferably selected from agents having a vanilla, banana, cherry, pineapple, chocolate, caramel, or mint flavour.

Preferably the composition also includes a lubricating system made up of a lubricating agent, a glidant and a flow agent. The lubricating agent is preferably selected from magnesium stearate, calcium stearate, stearic acid, and polyoxyethylene stearates. The preferred glidant is talc and the preferred flow agent is selected from silicone dioxide, fatty acid esters, and sodium lauryl sulphate.

In a second aspect of the invention there is provided a process for the preparation of a composition according to claim 1 including the steps:

(i) mixing the bitter tasting active ingredient with the lipid granulating agent and with the alkaline agent to give a granular matrix;

(ii) optionally further blending the granular matrix with one or more of a disintegrating agent, a sweetening agent, a flavouring agent, and a flow agent.

Preferably the granular matrix is prepared by hot melt spiral granulation. The hot melt spiral granulation may be carried out at any suitable temperature butis preferably carried out at a temperature below 80 ºC.

In one embodiment of the process the composition is compressed to provide water-dispersible tablets. In an alternative embodiment, the composition is not compressed to provide water-dispersible granules or powder.

DETAILED DESCRIPTION

The invention relates to dispersible compositions containing bitter alkaline drug substances including macrolide antibiotics, either alone or in combination with other active substances, and a process for the preparation of such compositions.

As used herein, the term "dispersible composition" means any solid dosage form, including tablets, granules, pellets, and powders, which disperses in water (including cold water) to form a suspension for drinking.

Any bitter tasting basic drug, or combination of bitter tasting drugs, is contemplated in this invention. However, the invention relates particularly to macrolide antibiotics, especially erythromycin, roxithromycin, azithromycin, and clarithromycin. The drug will typically be in the form of a stable hydrate, solvate, or salt, and may be in any crystalline or amorphous form. The azithromycin employed is preferably in form of isostructural pseudopolymorphs which exhibits superior dissolution properties as disclosed in Croatian Patent Application No. P20020231A.

The compositions of the invention include any dispersible composition, particularly granules, powders and tablets. Although tablets and capsules are simple to administer and convenient, children and elderly patients can have difficulty in swallowing them. For high dose drugs, size is a limitation. Dispersible pharmaceutical compositions are therefore convenient and easier to administer. Dispersible pharmaceutical compositions are also able to be titrated as required by patients.

The bitterness of the oral suspension formed when dispersible compositions of bitter drugs are dispersed in water is very difficult to mask. Dispersible pharmaceutical compositions made in accordance with the present invention reduce bitterness and do not hamper the dissolution characteristics of the drug substance, even when compressed. The compositions meet the requirements of the British Pharmacopoeia for dispersible pharmaceutical compositions including 'dispersible tablets'.

The granular matrix of a dispersible pharmaceutical composition can be prepared by a number of methods. One preferred method is the process of hot melt spiral granulation. The use of a traditional fluid bed dryer is known for developing 'granules with reduced bitterness'. Other equipment, such as intensive mixers and blending equipment with hot air provisions, may also be used for the same purpose. The drying temperature of the powder bed can be kept between 65 ºC to 70 ºC when a fatty acid ester such as glycerol dibehenate or glycerol distearate is used to illustrate the invention.

Hot melt spiral granulation has advantages over spray drying, microencapsulation and even particle coating or encapsulation technologies which require specialized equipment. The technique is environmentally friendly, reproducible and scalable.

The granulation agent used to form the granular matices by hot melt granulation is a lipid. The lipid may be a wax, oil, fatty acid, fatty alcohol, monoglyceride, diglyceride, or triglyceride. Carbon chain lengths are typically C12-C30 and they may be saturated or unsaturated. Examples include glycerol monostearate, glycerol distearate, glycerol behenate, glycerol dibehenate, and glycerol palmitostearate. The lipid may also be hydrogenated castor oil, a cetomacrogol emulsifying wax, carnuba wax, cetyl alcohol, or a cetyl ester. It is to be appreciated that any suitable combination of two or more lipids may be used.

The preferred lipid is normally solid at room temperature (18-22 °C), but desirably melts readily with the application of mild temperatures (i.e. about 55-

95 °C). Mixtures, whose components may individually fall outside this melting temperature range, but whose average melting point is within this range, are also included.

The applicant has surprisingly found that the preferred lipid amount is as low as 1 to 16 %, preferably 2 to 8%, by weight of the active pharmaceutical ingredient. The key advantage of keeping the amount of lipid as low as possible is that the affect on drug dissolution/release is minimised while still reducing the bitter taste of the drug.

A wetting agent, such as sodium lauryl sulphate, is preferably incorporated (not more then 2% for granules with reduced bitterness). Other wetting agents include docusate sodium, polysorbates, and sorbitan fatty acid esters. A wetting agent is dispersion aid. When used in small quantities, wetting agents generally help with dispersion of tablets and with dissolution.

To stabilize the pH of the composition, an alkaline substance such as sodium carbonate or tri-basic sodium phosphate is added in the amount of 1 to 20 %, preferably 2 to 14 %, in the anhydrous form, by weight of the active pharmaceutical ingredient. Intra-granular and extra-granular addition of alkaline substances have been evaluated and both reduce the bitterness of the dispersible compositions. Alkaline substances that dissolve rapidly when the dispersible composition is added to water aid in the formation of a uniform dispersion. Typical alkaline agents include sodium carbonate, potassium carbonate, sodium phosphate, potassium phosphate, sodium hydroxide, and potassium hydroxide.

Other excipients used alone or in combination can be added to improve the flow properties of the dispersible compositions. These diluting agents include cellulose, microcrystalline cellulose, mannitol, sorbitol, starch, pre-gelatinized starch, gelatinized starch, directly compressible microcrystalline cellulose, lactose, calcium carbonate, silica, and dibasic calcium phosphate.

Preferred compositions of the invention utilize diluting granules that consist of a blend of microcrystalline cellulose and maize starch in various ratios from

1:3 to 3:1 with the preferred range of 1.25:1.0 to 1.75:1.0. Ethyl cellulose (2 to 10 %) in the form of an aqueous dispersion with a plactisizer (e.g. Surelease™) may be used as a granulating agent for the diluting granules. The excipient combination has been evaluated for compressibility of the blend formed when mixed with the granular matrix with reduced bitterness. The disintegration and flow properties of the dispersible pharmaceutical compositions of the invention are improved when these diluting granules are used.

The granular matrix of the bitter tasting active ingredient may be further processed into dispersible dosage forms using diluting granules and other diluting substances. The granules of diluting agent have good flow properties, compressibility and disintegration characteristics. Surprisingly, investigations found that the cationic polymer amino alkyl methacrylate copolymer E (Eudragit™ E, EPO) is a suitable disintegrating agent in the dispersible dosage composition. Amino alkyl methacrylate copolymer E is poly (butyl methacrylate, (2-dimethyl amino ethyl) methacrylate, methyl methacrylate 1:2:1. Other disintegrating agents include carmellose sodium, croscarmellose sodium, sodium starch glycolate, crospovidone, and Polacrillin potassium.

A sweetening agent, such as aspartame, ammonium glycerrhizinate (e.g. magnasweet™), saccharin sodium and other saccharides, acesulfame potassium, or mannitol, is preferably incorporated as a secondary sweetener. The use sweetening agents in high dose is undesirable because of unpleaseant aftertastes and generally to avoid giving patients unnecessary amounts of additives. In the present invention a low level (2 to 5%) of sweetening agent is preferably added to provide a sweet taste. Aspartame is preferred as the sweetening agent for dispersible compositions such as tablets.

Selecting a flavouring agent for an alkaline bitter drug is difficult. Citrus flavours are not useful as they impart a bitter taste whereas some other flavours, such as mint and vanilla, synergistically reduce the bitterness of preparations. Flavouring agents evaluated are vanilla, banana, cherry, pineapple, caramel, chocolate, mint and related flavouring compounds.

Formulations with acceptable tastes were obtained with mild flavours and also when no flavouring agent was added.

The incorporation of a lubricating agent, such as magnesium stearate or calcium stearate, or related pharmaceutically acceptable lubricating compounds, is preferable. Magnesium stearate is preferred as the most commonly used agent in pharmaceutical compositions. A flow agent, such as silicone dioxide, and an anti-adhesive agent (glidant), such as purified talc, are also preferred in the dispersible compositions of the invention.

The invention will be better understood by referring to the following examples of dispersible compositions. However, the examples are for illustrative purposes and it should be understood that the invention is not limited to these examples.

EXAMPLES

Example 1: Granular matrix with reduced bitterness

Ingredient	Quantity (mg)	Composition (% w/w)
Azithromycin (as isostructural pseudopolymorph) for 500 mg Azithromycin	528.26	89.63
Sodium lauryl sulfate	3.00	0.51
Tri-basic sodium phosphate (anhydrous)	36.98	6.27
Glycerol dibehenate	21.13	3.59
Total Weight	589.37	100.00

The granular matrix was prepared with azithromycin, glycerol dibehenate and sodium lauryl sulphate. Tri-basic sodium phosphate was added either intra-granularly in the granular matrix or externally in the dispersible composition. The granular matrix was examined using scanning electron microscopy (SEM).

Components were mixed and then granulated using a fluid bed processor with an attachment for spiral granulation. These granules were then used to prepare dispersible compositions.

Example 2: Granular matrix with reduced bitterness

Ingredient	Quantity (mg)	Composition (% w/w)
Azithromycin (as isostructural pseudopolymorph) for 500 mg Azithromycin	528.26	86.53
Sodium lauryl sulfate	3.00	0.49
Tri-basic sodium phosphate, anhydrous	36.98	6.06
Glycerol dibehenate	42.22	6.92
Total Weight	610.46	100.00

The granular matrix was prepared by intra-granular additional of glycerol dibehenate to give a matrix containing 8 % by weight of glycerol dibehenate. These granules with a higher amount of fatty acid esters showed good taste-masking. The granules were used for dispersible compositions without compression.

Example 3: Granular matrix with reduced bitterness

Ingredient	Quantity (mg)	Composition (% w/w)
Azithromycin (as isostructural pseudopolymorph) for 500 mg Azithromycin	528.26	89.63
Sodium lauryl sulfate	3.00	0.51

Tri-basic sodium phosphate (anhydrous)	36.98	6.27
Glycerol distearate	21.13	3.59
Total Weight	589.37	100.00

These granules were prepared with intra-granular or extra-granular use of tri-basic sodium phosphate. Glycerol distearate was used as the granulating agent. These granules can be used to form a variety of dispersible compositions.

Example 4: Diluting granules

Ingredient	Quantity (g)	Composition (% w/w)
Microcrystalline cellulose (Avicel PH 101)	240.00	57.69
Starch (Maize Starch)	160.00	38.46
Ethylcellulose (As Surelease)	16.00	3.85
Total weight	416.00	100.00

Diluting granules were prepared using microcrystalline cellulose (Avicel™ PH 101) and maize starch. The granulating agent used was an aqueous dispersion of ethylcellulose (Surelease™). Granules were dried at 60 ºC. Dried granules were sized to give fast disintegrating and flowing granules.

Example 5: Eudragit™ EPO as a disintegrating/dispersing agent in dispersible tablets

The granular matrix of Example 2 and the diluting granules of Example 4 were mixed. The granules were passed through a sieve (40#) and blended with other excipients: aspartame, a disintegrating/dispersing agent, tribasic sodium phosphate, anhydrous colloidal silica, and talc. The mixture was then lubricated with magnesium stearate. The following disintegrating/dispersing agents were used: aminoalkyl methacrylate copolymer E (Eudragit™ EPO), carmellose sodium, sodium starch glycollate, and polacrillin potassium.

Tablets were compressed using granules of dispersible compositions and evaluated for ease of dispersion by putting tablets in 60 ml water at 25 °C in a 150 ml glass beaker.

The results with carmellose cellulose, sodium starch glycollate and polacrillin potassium were not satisfactory. Some agglomerated tablet mass was observed at the end of 3 minutes in the beaker.

Eudragit™ EPO was used at 100 mg per tablet, good tablet dispersion was observed (see table below). These tablets complied with disintegration tests for tablets under dispersible tablets and uniformity of dispersion.

Evaluation of Eudragit™ EPO as disintegrating/dispersing agent

Amount (mg) of Eudragit™ EPO in formulation as per Example 6	Observations
0	Tablet dispersion was incomplete within 3 minutes.
50	Tablet dispersion was improved but incomplete within 3 minutes.
100	Tablet dispersion was complete within 1 to 3 minutes.
150	Tablet dispersion was complete within 1 to 3 minutes.

Example 6: Dispersible pharmaceutical composition such as tablets

Ingredient	Quantity/tablet (mg)	Composition (% w/w)
Granular matrix with reduced bitterness (for	552.41	43.33

500mg Azithromycin)		
Diluting granules	523.59	41.07
Aspartame	30.00	2.35
Aminoalkyl methacrylate copolymer E (Eudragit™ EPO)	100.00	7.84
Tri-basic sodium phosphate (anhydrous)	40.00	3.14
Anhydrous, colloidal silica	5.00	0.39
Talc	12.00	0.94
Magnesium stearate	12.00	0.94
Tablet weight	1275.00	100.00

The granular matrix of Example 1 and the diluting granules of Example 4 were mixed. The granules were passed through a sieve (40#) and blended with other excipients: aspartame, aminoalkyl methacrylate copolymer E (Eudragit™ EPO), tribasic sodium phosphate, anhydrous colloidal silica, and talc. The mixture was then lubricated with magnesium stearate.

Tablets were compressed using granules of dispersible compositions and evaluated for taste, uniformity of dispersion and other pharmacopoeial tests. Reconstituted tablets were found to be acceptable for taste as well as other tablet characteristics such as dissolution, assay, hardness, friability and ease of reconstitution.

Example 7: Evidence for masking of bitterness

Compositions for taste evaluation included granules containing azithromycin 500 mg, diluting granules (granules of starch and microcrystalline cellulose), aminoalkyl methacrylate copolymer E (Eudragit™ EPO), talc, colloidal silica and magnesium stearate. The level of fatty acid ester in the granules with reduced bitterness was varied as shown in the table below. The level of

tribasic sodium phosphate and aspartame was also varied as shown in the table below. Compositions were assessed in 5 volunteers.

Ingredients	Composition trials for taste evaluation							
	I	II	III	IV	V	VI	VII	VIII
Glycerol dibehenate	4%				4%	4%	4%	4%
Tribasic sodium phosphate anhydrous		7%	7%	7%			7%	7%
Aspartame (mg)			30	100	30	100	30	100
Preferred rating of Taste Evaluation	F	F	F	E	F	E	B	C

Percentage values are relative to the weight of azithromycin (as dehydrate)

The compositions were separately dispersed in 60 ml water and were evaluated for taste, immediately after dispersion.

Taste evaluation:

A: palatable, acceptable preparation

B: palatable, acceptable preparation with very low bitterness and very low aftertaste

C: palatable, acceptable preparation with low bitter taste and low aftertaste.

D: palatable, acceptable preparation with low bitter taste and unacceptable after taste.

E: Not palatable preparation due to bitter aftertaste and bitter taste.

F: Not palatable preparation due to very bitter taste.

The composition VII and VIII which contained fatty acid ester glycerol dibehenate, alkaline buffer salt sodium phosphate and sweetening agent aspartame were significantly better than I to VI. The composition VIII was too sweet and also exhibited a bitter after taste.

Example 8: Evidence for masking of bitterness

Compositions for taste evaluation included granules containing azithromycin 500 mg, diluting granules (granules of starch and microcrystalline cellulose), aminoalkyl methacrylate copolymer E (Eudragit™ EPO), talc, colloidal silica and magnesium stearate. The level of fatty acid ester in the granules with reduced bitterness and aspartame was fixed as shown in the table below. The level of tribasic sodium phosphate was fixed but used extra-granularly except in XI where it was used intra-granularly. Compositions were assessed in 5 volunteers.

Ingredients	Composition trials for taste evaluation			
	VII	IX	X	XI
Glycerol dibehenate	4%	4%	4%	4%
Sodium Phosphate tri-basic, anhydrous	7%	7%	7%	7% (intra-granular)
Aspartame (mg)	30	30	30	30
Vanilla (mg)	-	25	-	-
Banana (mg)	-	-	25	-
Preferred rating	B	C	C	B

Percentage values are relative to the weight of azithromycin (as dehydrate)

In the following table, composition XII is the same as VII without azithromycin. The taste of the dispersion was compared with composition VII without the drug azithromycin. The composition was marked as XII.

Preferred ratings of compositions VII, IX, X and XI by 20 volunteers.

Volunteer No	Compositions for taste evaluation				
	VII	IX	X	XI	XII
1	B	C	D	B	A
2	B	C	C	B	A
3	B	C	D	A	A
4	B	D	C	B	A
5	C	D	D	B	A

6	B	C	C	B	A
7	B	D	D	B	A
8	B	C	C	B	A
9	B	D	D	B	B
10	B	C	C	A	A
11	B	C	C	B	A
12	B	D	D	B	A
13	B	C	C	B	A
14	B	D	D	B	A
15	A	C	D	B	A
16	B	C	C	B	A
17	B	C	C	B	A
18	B	C	C	B	A
19	B	C	C	A	A
20	B	D	D	B	A
Preferred rating	B	C	C	B	A

Taste evaluation:

A: palatable, acceptable preparation

B: palatable, acceptable preparation with very low bitterness and very low aftertaste

C: palatable, acceptable preparation with low bitter taste and low aftertaste.

D: palatable, acceptable preparation with low bitter taste and unacceptable aftertaste.

E: Not palatable preparation due to bitter aftertaste and bitter taste.

F: Not palatable preparation due to very bitter taste.

Observations:

Volunteers showed acceptance level for these formulations of azithromycin. Acceptability for compositions without flavouring components was more than that for the compositions with flavouring components such as vanilla and banana indicating flavouring was non-obligatory for these types of formulations. Sodium phosphate tri-basic, anhydrous when used intra-granularly with fatty acid esters exhibited marginally better acceptance.

Although the invention has been described by way of example, it should be appreciated that variations or modifications may be made without departing from the scope of the claims. Furthermore, where known equivalents exist to specific features, such equivalents are incorporated as if specifically referred to in this specification.

CLAIMS

1. A dispersible pharmaceutical composition including:
   (i) a bitter tasting active ingredient;
   (ii) a lipid granulating agent in the amount of 1 to 16 % by weight of the active ingredient; and
   (iii) an alkaline agent in the amount of 1 to 20 % by weight of the active ingredient;
   where the bitter taste of the active ingredient is partially or completely masked.

2. A composition according to claim 1 where the bitter tasting active ingredient is a macrolide antibiotic.

3. A composition according to claim 2 where the macrolide antibiotic is selected from erythromycin, clarithromycin, roxithromycin, and azithromycin, including and preferebly azithromycin in the form of isostructural pseudopolymorph which exhibits superior dissolution properties (as one disclosed in Croatian Patent Application No. P20020231A.)

4. A composition according to any of claims 1 to 3 where the lipid granulating agent is in the amount 2 to 8 % by weight of the active ingredient.

5. A composition according to any one of claims 1 to 4 where the lipid granulating agent is a wax, fatty acid, fatty alcohol or is a mono-, di-, or tri-glyceride of one or more fatty acids.

6. A composition according to claim 5 where the lipid granulating agent is selected from glycerol mono-, di-, and tri-stearate, glycerol mono-, di-, and tri-palmitostearate, glycerol mono-, di-, and tri-behenate, glycerol mono-, di-, and tri-oleate, hydrogenated castor oil, a cetomacrogol emulsifying wax, carnuba wax, cetyl alcohol, and a cetyl ester.

7. A composition according to any one of claims 1 to 6 where the alkaline agent is in the amount 2 to 12 % by weight of the active ingredient.

8. A composition according to any one of claims 1 to 7 where the alkaline agent is selected from sodium carbonate, potassium carbonate, sodium phosphate, potassium phosphate, sodium hydroxide, and potassium hydroxide.

9. A composition according to any one of claims 1 to 8 further including a surface active agent in the amount of not more than 2 % by weight of the active ingredient.

10. A composition according to claim 9 where the surface active agent is selected from sodium lauryl sulphate, docusate sodium, polysorbates, and sorbitan fatty acid esters.

11. A composition according to any one of claims 1 to 10 further including a diluting agent in the amount of 5 to 60% by weight of the total composition.

12. A composition according to claim 11 where the diluting agent is selected from cellulose, microcrystalline cellulose, lactose, mannitol, sorbitol, starch, calcium carbonate, dibasic calcium phosphate, silica, and pre-gelatinized starch.

13. A composition according to claim 11 where granules of diluting agent are prepared using a combination of microcrystalline cellulose and starch in a ratio from 1:3 to 3:1, and a water insoluble cellulose.

14. A composition according to claim 13 where the water insoluble cellulose is ethyl cellulose in the amount of 2 to 10 % by weight of the granules.

15. A composition according to claim 13 where the microcrystalline cellulose and starch are in a ratio from 1.25:1 to 2:1.

16. A composition according to any one of claims 1 to 15 further including a disintegrating agent in the amount of 1 to 12 % by weight of the total composition.

17. A composition according to claim 16 where the disintegrating agent is selected from carmellose sodium, croscarmellose sodium, sodium starch glycolate, crospovidone, aminoalkyl methacrylate copolymer E, and Polacrillin potassium.

18. A composition according to claim 17 where the disintegrating agent is cationic polymer aminoalkyl methacrylate copolymer E.

19. A composition according to any one of claims 1 to 18 further including a sweetening agent in the amount of 1 to 10% by weight of the total composition.

20. A composition according to claim 19 where the sweetening agent is selected from aspartame, coated aspartame, ammonium glycerrhizinate, saccharin sodium, acesulfame potassium, and sugars.

21. A composition according to any one of claims 1 to 20 further including one or more flavouring agents in the amount of 1 to 6% by weight of the total composition.

22. A composition according to claim 21 where the one or more flavouring agents are selected from agents having a vanilla, banana, cherry, pineapple, chocolate, caramel, or mint flavour.

23. A composition according to any one of claims 1 to 22 further including a lubricating system made up of a lubricating agent, a glidant and a flow agent.

24. A composition according to claim 23 where the lubricating agent is selected from magnesium stearate, calcium stearate, stearic acid, and polyoxyethylene stearates.

25. A composition according to claim 23 where the glidant is talc.

26. A composition according to claim 23 where the flow agent is selected from silicone dioxide, fatty acid esters, and sodium lauryl sulphate.

27. A process for the preparation of a composition according to claim 1 including the steps:

(i) mixing the bitter tasting active ingredient with the lipid granulating agent and with the alkaline agent to give a granular matrix; and

(ii) optionally incorporating wetting agent and further blending the granular matrix with one or more of a disintegrating agent, a sweetening agent, a flavouring agent, and a flow agent.

28. A process according to claim 27 where the granular matrix is prepared by hot melt spiral granulation.

29. A process according to claim 28 where the hot melt spiral granulation is carried out at a temperature below 80 ºC.

30. A process according to any one of claims 27 to 29 where the composition is compressed to provide water-dispersible tablets.

31. A process according to any one of claims 27 to 29 where the composition is not compressed to provide water-dispersible granules or powder.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR 03/00013

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 475 510 B1 (PALEPU NAGESWARA R ET AL) 5 November 2002 (2002-11-05)	1
A	column 5, line 31-53; claim 1 column 6, line 24	2-31
A	EP 1 161 956 A (DAIICHI SEIYAKU CO) 12 December 2001 (2001-12-12) paragraph '0017!; claims 1,6,10	1-30
A	US 5 380 535 A (GEYER ROBERT P ET AL) 10 January 1995 (1995-01-10) cited in the application column 5, line 42-57 column 6, line 16-28; example 3	1-30

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2003	01/10/2003

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/HR 03/00013

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 633 006 A (CATANIA JOSEPH S ET AL) 27 May 1997 (1997-05-27) cited in the application claim 2; tables 46-59 column 4, line 50-60 column 5, line 36-44; example 7	1-30.

INTERNATIONAL SEARCH REPORT

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